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ORIGINAL ARTICLE

The Role of CD58 and CD38 in Evaluation of Minimal Residual Disease in Childhood B-Acute Lymphoblastic Leukemia

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ABSTRACT

Background: Measurement of minimal residual disease (MRD) reflects the overall response to therapy and could be used to refine the treatment of acute lymphoblastic leukemia (ALL). MRD studies by flowcytometry rely on panels of antibodies (Abs) to define the unique immunophenotypic signature of leukemic blasts. This study aimed to evaluate the role of CD38 and CD58 in the detection of MRD in childhood B-ALL.

Methods: MoAb combinations were used to determine leukemia-associated immunophenotypic pattern specific for the patients (LAIP), which was used as a fingerprint in follow-up samples. LAIP was identified to allow the discrimination of leukemic blasts from normal lymphocyte progenitors and relies on qualitative or quantitative differences in antigen expression between leukemic cells and their normal counterparts. The LAIP present in an individual case has been identified by using multi-florescence colors (MFC) with a comprehensive panel of combinations of monoclonal antibodies, So MRD during the course of treatment and follow-up can be assessed by the quantification of the frequencies of these cells by MFC.

Results: The mean age in our patients was 6.7 years. They were 54% males and 46% females. On day 14 post-induction, 25% of our patients were negative for MRD, while 75% were positive for MRD. CD38 under-expression was +ve in 66.7%, while CD58 overexpression was +ve in 50% of the patients at diagnosis. There was a significant increase in +ve CD38 under-expression among patients who had +ve MRD. Also, there was a significant increase in +ve CD58 overexpression among patients who had -ve MRD. CD38 under-expression was demonstrated more than CD58 overexpression.

Conclusions: CD38 is a hopeful marker that needs to be used routinely for the assessment of MRD. It is more informative than CD58 in B-ALL patients. CD38 under-expression has a higher frequency and less modulation than CD58 overexpression during remission induction therapy.

Keywords: Minimal residual disease; Acute lymphoblastic leukemia; Flowcytometry; CD38; CD58

INTRODUCTION

ALL is the most common cancer in childhood representing twenty-five percent of cancer diagnosed between 2 and 5 years old. Due to the application of risk-adapted therapy, the 5 years survival rate has significantly increased to 92% over time. Though, relapses still occur in 20% of patients and are associated with a poor prognosis [1].

MRD is defined as the presence of residual leukemic cells in patients with complete hematological remission (CR) below 5%, which is the detection level of microscopy [2]. These residual leukemic cells which persist after induction of chemotherapy have a prognostic significance [3]. Negative MRD is a significant indicator of increased overall survival [4].

Different methods that assay MRD for ALL shall detect one leukemic blast among 10,000 normal cells or more in all patients. The most commonly used methods to study MRD in ALL are multi-parametric flowcytometry

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(MFC) of leukemia-associated immunophenotypic pattern (LAIP) and, polymerase chain reaction (PCR) amplification-based methods that use either leukemia-specific or patient-specific molecular markers [1].

Flowcytometry depends on using panels of antibodies (Abs) to identify the specific immunophenotypic (IPT) signature of leukemic blasts which must distinguish these blasts from their normal counterparts "hematogones"[5].

Detection of MRD in B-lineage ALL requires a larger panel of Abs. We usually identify immature B cells by the simultaneous expression of CD19, CD10, and CD34 or TdT [6]. Blasts are traced by a fourth color expression either in the form of over or under expression as in the case of (CD45, CD22, CD38, CD58) or other markers not expressed normally on B-cell progenitors as (CD13, CD33, CD65, CD66) or presence of asynchronous marker expression as in case of CD21 and others [7].

CD58 was reported to be overexpressed in cases of B-ALL [8], while CD38 was often under-expressed [9]. We aimed to evaluate the role of CD38 and CD58 in the detection of MRD in childhood B-ALL.

METHODS

Subjects:

The present study was done at the clinical pathology department and pediatrics department of Zagazig university hospitals during the period between January 2017 and June 2018. Forty-eight (48) Patients with B-Acute lymphoblastic leukemia shared in the present study. The range of the patients' ages was from 1 to 17 years with a mean ± SD of 6.7 ± 4.83 years and the median was 6 years. They were 26 (54%) males and 22 females (46%) with a male to female ratio of 1.18:1.

For controls, bone marrow was aspirated from 12 patients with non-hematological malignancies but needed bone marrow aspiration as a routine investigation, e.g., Idiopathic thrombocytopenic purpura (ITP) and hypersplenism. Control samples were used to determine the mean fluorescence of intensity (MFI) of CD58 and CD38 of hematogones and identify the cutoff value of underexpression and overexpression. According to the ROC curve, the points with the highest sensitivity and specificity, cut off for MFI of CD58 was (72.1), and MFI of CD38 was (43.7) for hematogones.

Inclusion criteria:

Newly diagnosed cases of B-lineage ALL. Written consent by patients' parents to share in the thesis and approval to share in the study.

Exclusion criteria:

Previously diagnosed patients on chemotherapy and patients' refusal.

Methods:

All patients were subjected to the followings: Thorough history taking, full clinical examination, and routine laboratory investigations as the following: complete blood picture using an automatic cell counter (Sysmex XT1800 i), peripheral blood examination of Leishman-stained films, Liver and Kidney function tests, and LDH level estimation using an autoanalyzer (Cobas Integra 400 plus). Bone marrow aspiration was done with an examination of Leishman-stained films and myeloperoxidase-stained films. Immunophenotyping of EDTA bone marrow (BM) samples was performed on Becton Dickinson (BD, FACSCalibur; San Jose, California, USA). Acute leukemia panel: CD3, CD5, CD7, CD10, CD13, CD14, CD19, CD20, CD22, CD33, CD34, CD64, CD79a, TDT, HLA-DR and MPO was used. The cutoff for the marker positivity was >20% of the cells expressing this marker except for TDT and CD34, which was 10%.

Special Investigations:

The panel consisted of 2 tubes each with 4 monoclonal antibodies; CD58APC and CD38APC in combination with CD10FITC, CD19PE, and CD34Percp were identified at day 0 and at day 14 post-induction for assay of minimal residual disease.

Sampling:

One milliliter of peripheral blood was aseptically collected on K-Ethylene Diamine Tetra Acetic Acid (K-EDTA) for CBC and preparation of Leishman-stained PB smears. Peripheral blood films were prepared for

Leishman & cytochemical staining. One milliliter of BM sample on EDTA was used for immunophenotyping and flow cytometric detection of B-lymphoid markers (CD10, CD19, CD34) and CD58 or CD38 as a fourth color. Five hundred microliters of BM sample were used for detection of minimal residual disease (MRD) on day 14 post-induction using Mo Abs (CD10, CD19, CD34) and CD58 or CD38 as a fourth color as defined at diagnosis. Sera were collected for routine liver, kidney, and LDH estimation.

Methodology of detection of Minimal residual disease:

At diagnosis, MoAb combinations were used to determine leukemia-associated immunophenotypic pattern specific for the patients (LAIP), which was used as a fingerprint in follow-up samples. LAIP was identified to allow the discrimination of leukemic blasts from normal lymphocyte progenitors and relies on qualitative or quantitative differences in antigen expression between leukemic cells and their normal counterparts. The LAIP present in an individual case has been identified by using multi-florescence colors (MFC) with a comprehensive panel of combinations of monoclonal antibodies, So MRD during the course of treatment and follow-up can be assessed by the quantification of the frequencies of these cells by MFC [10].

Sample Preparation:

For each patient, 50,000 events were acquired for identifying LAIP at diagnosis, while 500,000 events were acquired for diagnosis of MRD in each tube.

Detection of Surface Markers:

All used tubes (12 X 75 mm) must be labeled with a Lab code and monoclonal antibody including control tubes. One hundred microliters of sample were added to all labeled tubes. Ten µl of each MoAb as well as of the isotypic negative control were added to the respective tubes. All tubes were vortexed and incubated in the dark at room temperature for 15-20 minutes. One ml of 1x10 lysing solution (BD) was added to each tube, vortex, and incubated for 10 minutes at room temperature. Centrifuge at 1500 rpm was done for 5 minutes and the supernatant was discarded. The washing step using 1ml PBS was performed twice. Cells were suspended in 500µl PBS to be ready for acquisition using the CellQuest software (BD, San Joes, USA).

Analysis of MRD:

Analysis of samples was done by multicolor flowcytometry (FACS Calibur flow cytometer (BD, San Joes, USA).

Gating strategy:

MRD detection is done by using a sequential gating strategy. First, lympho-population gating was applied on SSC vs FSC and CD19/CD34 coexpressing population, then CD19/CD10 coexpression, then gating on (CD34/CD58) and (CD34/ CD38) respectively. Leukemic cells were detected at a dot plot and the number of blasts was estimated from statistics. Samples were considered to be MRD positive if the quantification of MRD was ≥0.01% [11].

Statement of ethics:

This study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1964, as revised in 2000, and was approved by the institutional review board of the faculty of medicine, Zgazig University. Informed consent was gotten from all study participants and/or their caregivers. IRB (Institutional Review Board) approval number is ZU#IRB1762(24/12/2014).

Satistical analysis:

The collected data were computerized and statistically analyzed using the SPSS program (Statistical Package for Social Science) version 25. Qualitative data were represented as frequencies and relative percentages. The Chi-square test was used to calculate the difference between qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation). P-value of >0.05 indicates non-significant results. P-value of <0.05 indicates significant results.

RESULTS

The mean age in our patients was 6.7 ± 4.83 years. They were 54 % males and 46% females. The demographic characteristics of patients were listed in table 1. On day 14 post-induction, 25% of our patients were negative for MRD, while 75% were positive

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for MRD (table 2). CD38 under-expression was +ve in 66.7%, while CD58 overexpression was +ve in 50% of the patients at diagnosis (table 3). There was a significant increase in +ve CD38 under-expression among patients who had +ve MRD. Also, there was a significant increase in +ve CD58 overexpression among patients who had -ve MRD (table 4). CD38 underexpression demonstrated a higher frequency of retention (FOR), higher frequency of gain (FOG), and lower frequency of loss (FOL) than CD58 overexpression (table 5).

Table 1: Socio-demographic characteristics of our patients.

Variable		(n=48)	
Age(years)	Mean ± SD Median Range	6.70 ± 4.83 6 1 - 17	
Variable		No	%
Age risk group	Favorable >1-<10 unfavorable ≤1-≥10	34 14	70.8 29.2
Sex	Male Female	26 22	54.2 45.8

SD: Standard Deviation

Table 2: MRD among our patients at day14 post induction.

Variable		(n=48)
MRD	Mean ± SD Median (Range)	0.22 ± 0.42 0.07 (<0.01-2.39)
	-ve (<0.01) +ve (≥0.01) – 0.1 >0.1	12 (25%) 36 (75%) 14 (29.2%) 22 (45.8%)

SD: Standard Deviation

Table 3: Frequency of CD38 under-expression and CD58 overexpression among our patients' pretreatment.

Variable		Pretreatment (n=48)	
		No	%
CD38	+ve -ve	32 16	66.7 33.3
CD58	+ve -ve	24 24	50 50

Table 4: Relation between prognosis and CD38 under-expression and CD58 overexpression among the studied patients' pretreatment.

Variable		MRD				χ^2	P
		-ve (n=12)		+ve (n=36)			
		No	%	No	%		
CD38 underexpression	+ve -ve	0 12	0 100	32 4	88.9 11.1	31.98	<0.001 **

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CD58 overexpression	+ve	12	100	12	33.3	15.99	<0.001 **
	-ve	0	0	24	66.7		

χ2: Chi-square test, **: Highly significant (P<0.01)

Table 5: Relation between MRD and Stability of CD38 under-expression and CD58 overexpression among the patients.

Variable			MRD -ve (n=12)		MRD +ve (n=36)	
			N	%	N	%
CD38	Pre treatment	+ve	0	0	32	88.9
		-ve	12	100	4	11.1
	Stability	Remain +ve (FOR)	0	0	26	72.2
		Loss (FOL)	0	0	6	16.7
		Remain -ve	12	100	0	0
		Gain (FOG)	0	0	4	11.1
	Post treatment	+ve	0	0	30	83.3
		-ve	12	100	6	16.7
CD58	Pre treatment	+ve	12	100	12	33.3
		-ve	0	0	24	66.7
	Stability	Remain +ve (FOR)	0	0	6	16.7
		Loss (FOL)	12	100	6	16.7
		Remain -ve	0	0	22	61.1
		Gain (FOG)	0	0	2	5.6
	Post treatment	+ve	0	0	8	22.2
		-ve	12	100	28	77.8

FOR: Frequency of retention; FOL: Frequency of loss; FOG: Frequency of gain

DISCUSSION

Days 8 and 15 post-induction are used as early checkpoints to evaluate the patients' sensitivity to the therapy in different ALL protocols [12].

Measurement of MRD by flow cytometry is based on the principle that leukemic cells present unusual antigenic patterns that separate them from maturing precursor cells i.e. hematogones. Alternatively, polymerase chain reaction (PCR) DNA sequences specific to leukemia are identified and amplified. These techniques reliably detect the presence of at least one in 10,000 leukemic cells in flow cytometry and one in 100,000 in PCR amongst normal bone marrow mononuclear cells. Flow cytometry has a comparatively faster turnaround time, is cost-effective, and is less labor-intensive. Thus, flow-based MRD assessment has the potential for rapidly identifying patients at increased risk of relapse, allowing for prompt modifications in therapy, including earlier intensification [13].

The approach used in this study was to assess the role of CD58 and CD38 in the evaluation of MRD in childhood B-ALL in combination with CD10, CD19, and CD34.

Blasts are traced by abnormal expression of CD38 and CD58 based on their deviation from normal B cell precursors (hematogones). Overexpression of CD58 and under-expression of CD38 were considered as leukemia associate immunophenotype "LAIP" [14].

In the current study, results of minimal residual disease status (MRD) of ALL patients at day 14-post induction revealed that 25% of our patients had -ve MRD (<0.01), 29.2% had positive MRD (between 0.01-0.1) and 45.8% of patients had MRD level ≥0.1.

The twelve patients (25%) with negative-MRD had (in complete remission) blast cells by immunophenotyping less than 0.01% and by morphology, blasts were absent (0%). In thirty-four cases (70.8%) there was a difference between BM blast count by morphology and

immunophenotyping at day 14. Blast cells by morphology were 0.0% and by immunophenotyping ranged from 0.01-0.06%, blast cells by morphology were 1- <5% and by immunophenotyping ranged from 0.03-0.91%. Two (4.2%) patients were Positive for MRD, blast cells by morphology were ≥5%. These two patients were CD38 positive on day 0 and day 14. This supports the recommendation to decrease the level of the blast cells to <1% as complete hematological remission. These data were in agreement with Baraka et al [10].

As shown by Bjorklund et al [15], MRD was revealed to be prognostic at each time point evaluated. However, the best assay points seemed to be early in therapy and early in consolidation.

The choice of day fourteen post-induction to evaluate MRD was compatible with Neale et al [16] who investigated the most informative time points for MRD testing and illustrated that measuring of MRD two weeks after induction of therapy can early differentiate between good and poor responders to chemotherapy.

Also, the choice of day fourteen post-induction to evaluate MRD was compatible with Short et al [17] who reported that Day 14 BM blasts were strongly prognostic for the achievement of CR. The assessment of D14 BM blasts may be useful for risk stratification and for guiding post-induction treatment.

Being the limit of detection for flowcytometric and molecular assays, the 0.01% detection limit was used to determine MRD positivity. This 0.01% level was proved to be clinically informative [18].

In the current study, CD38 in combination with CD10, CD19, and CD34 were informative in 70.8% of studied patients at diagnosis, and CD58 in combination with CD10, CD19, and CD34 were informative in 60.4% of studied patients which let us use these combinations for further valuation of MRD at day 14.

The choice of the combination of CD38/CD10/CD19/CD34 for detection of MRD was compatible with Xia et al [19], who informed that the most appropriate MoAb combinations were TdT/CD10/CD34/CD19 (87/139, 62.6%), then CD38/CD10/CD34/CD19 (85/139, 61.2%).

Also, the choice of combination of CD58/CD10/CD19/CD34 was compatible with Baraka et al. [14], who informed that CD58/CD10/ CD19/CD34 was informative in 59.5% of studied cases. Also, Xu et al [20], demonstrated that The CD58/ CD10/ CD34/ CD19 was the second appropriate combination for measuring of MRD in ALL patients by flowcytometry after TdT/ CD10/ CD34/ CD19. CD58 might be used as a marker for enriching the combinations of MRD assessments. Also, this agreed with Lui et al [21].

In the current study, under-expression of CD38 was found in 66.7% of patients. This was in agreement with Tembhare et al [22] who found CD38 under-expression in 70.2% of BCP-ALL patients, and Karawajew et al [23] who found the expression of CD38 was lower on blasts than on hematogones in 67% of ALL cases and reported that CD38 is the most promising marker for discriminating normal and leukemic $CD10^+$ B-cell progenitors. Also, Patkar et al [24] detected aberrancies of CD38 in 66.7% at diagnosis and this was a useful tube to detect MRD at both mid and end induction time points. In addition to Irving et al [11] who found CD38 applicability in 63%, Krampera et al [25] in 57% of patients, and Lucio et al [26] found CD38 aberrancies in 55.6% of BCP-ALL. Whereas Campana et al [6] found under-expression of CD38 has applicability in 30–50% of patients.

In the current study, overexpression of CD58 was found in 24 (50%) of patients, this was in agreement with Tembhare P et al [22], who found CD58 overexpression in 46.4% of BCP-ALL patients. Also, Baraka et al [10] reported that CD58 overexpression was found in 37.3% of the patients. Xu et al [20] reported that CD58 overexpression was detected in 51.9% of the patients. Li et al [27], reported that CD58 was over-expressed in 44 of the total studied 87 patients (50.5%) of the B-ALL cases.

This result disagreed with Veltroni et al [28], who presented that CD58 had significantly higher expression in ALL blasts when compared with normal B lymphocytes. But, no difference was observed between regenerating

and normal B lymphocytes. CD58 was positive in 99.4% of the B-ALL patients and was overexpressed in 93.5% of them compared to normal.

In the current study, there was a highly significant increase in +ve CD38 under expression among cases who had +ve MRD (88.9%), indicating that underexpression of CD38 is associated with poor prognosis in B-ALL patients.

This finding agreed with Cruz-Rodriguez et al [29] who reported that individuals of ALL who had tumoral lymphoblasts with lower expression of CD19, CD38, and CD45 and high expression of CD10 had poor prognosis and low EFS. This group of patients had low CR rates and a high percentage of MRD+.

Also, our results agreed with Wilson K et al [30] who reported in their study on 48 children with B-ALL, where CD38 underexpression patients appeared to have a higher rate of MRD positivity. This observation required validation in a large cohort group, but it was supported by findings that high CD38 expression is associated with a favorable prognosis in both adult AML and ALL.

In the current study, there was a significant decrease in +veCD58 overexpression among cases who had +ve MRD (33.3%), indicating that CD58 overexpression is associated with a good prognosis in B-ALL cases.

These results agreed with Xu et al [20] who demonstrated that the rate of MRD diagnosis by flowcytometry was significantly low in CD58 overexpression cases ($p<0.05$). The CD58 overexpression could be a marker of better prognosis in children with B-ALL.

In the current study, the sensitivity of CD38 under-expression in the prediction of outcome was 88.9%, specificity was 100% and accuracy was 91.7%. There was a significant agreement between MRD&CD38, while the sensitivity of CD58 overexpression in the prediction of outcome was 33.3%, specificity was 0.0% and accuracy was 25%. There was no significant agreement between MRD & CD58. CD38 has higher sensitivity and specificity than CD58 in the prediction of outcome in the studied group of patients.

This result agreed with Karawajew et al [23] who reported that there were considerably fewer MRD-negative samples(35.6% vs 52.8%) and more positive samples (14.4% vs 3.1%) using the CD38-tube in comparison with CD58-tube.

Our results showed that there was a significant decrease in CD58 MFI among the studied cases on day 14 compared to day 0, but no difference was found in CD38 MFI post-induction compared to day 0.

In addition, we studied the immunophenotypic shift of abnormal expression of markers, CD38 and CD58, in day14 MRD positive samples. The frequencies of LAIPs, under-expression of CD38, and Overexpression of CD58 were demonstrated in leukemic blasts from diagnostic samples and MRD positive samples (36). In these 36 samples, the frequency of LAIP at diagnosis was higher for CD38 (88.8%) than CD58 (33.3%). On studying frequency of retention (FOR) in MRD samples, CD38 demonstrated higher FOR (81.2%) of LAIP than CD58 (50%). On studying the frequency of gain (FOG), CD38 demonstrated higher FOG (25%) than CD58 FOG (8.3%). CD38 has frequent of loss (FOL) (18.7%) lower than CD58 (50%).

These results indicated that CD38 has better stability and less therapy-induced immunophenotypic shift than CD58.

These results were compatible with Tembhare et al [14], who informed that among the studied 10 markers CD38 was one of the most stable markers with the high FOR (83.5%) and low FOL (16.5%). CD58 showed a notable immunophenotypic shift with high FOL (31.6%) and low FOR (68.4%). Overall, data demonstrated that CD73, CD38, CD123, and CD86 were the most useful markers in MRD detection.

On the contrary, Velroni et al [28] reported that no significant change in CD58 expression during chemotherapy was detected and confirmed its stability and accuracy in MRD assessment.

CONCLUSION

CD38 is a hopeful marker that needs to be used routinely for the assessment of MRD. It is more informative than CD58 in B-ALL patients.

CD38 under-expression has a higher frequency and less modulation than CD58 overexpression during remission induction therapy. CD38 under-expression may be considered as a marker of an unfavorable outcome, while CD58 overexpression is a marker of good prognosis in BCP-ALL. It can be used with CD10, CD19, CD34, or other combinations.

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